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Review article

Combined liver-lung transplantation: Indications, outcomes, current experience and ethical Issues

Jing L. Han [a], Eliza W. Beal [a], Khalid Mumtaz [b], Ken Washburn [c], Sylvester M. Black [a,c,*]

[a] Department of Surgery, The Ohio State University Wexner Medical Center, Columbus, OH, United States
[b] Division of Gastroenterology, Hepatology and Nutrition, The Ohio State University Wexner Medical Center, Columbus, OH, United States
[c] Division of Transplantation Surgery, Department of Surgery, The Ohio State University Wexner Medical Center, Columbus, OH, United States

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ABSTRACT

Combined liver-lung transplantation (CLLT) is a rare, life-saving procedure to treat concomitant lung and liver disease. There have been 93 combined lung and liver transplantations performed in the United States since 1994. Techniques include both lung first and liver first sequential transplants with selective extracorporeal circulation of either thoracic or abdominal portions, with either end-to-end or Roux-en-Y choledochojejunostomy for biliary reconstruction. This review evaluates the existing literature regarding combined lung and liver transplantation (CLLT), describing the candidates, operation, perioperative complications, associated management strategies, and recommendations for immunosuppressive therapy and follow up.

Contents

1. Introduction

There have been 103 combined lung and liver transplantations (CLLT) performed in the United States to date, the first performed in 1994 at the University of Illinois Medical Center. In the decade following this inaugural operation, only 17 CLLT were performed, and it remains a relatively rare procedure [1], comprising <0.01% of the 12,749 multiorgan transplants that have occurred in the United States since 1988 (Fig. 1) [2]. These 103 surgeries were all performed at high-volume centers: Houston Methodist Hospital (14), Duke University (15), Cleveland Clinic Foundation (10), University of Pennsylvania (10), St. Louis Children's Hospital (7), Texas Children's (7), and University of Pittsburg (7), while the remaining 21 centers performed 5 or fewer CLLT each [1]. There is a dearth of published literature on CLLT,

Abbreviations: AATD, Alpha-1 antitrypsin deficiency; AKI, Acute kidney injury; CF, Cystic fibrosis; CLLT, Combined lung liver transplant; CMV, Cytomegalovirus; COPD, Chronic obstructive pulmonary disease; CPB, Cardiopulmonary bypass; EACA, Epsilon-aminocaproic acid; ECMO, Extracorporeal membrane oxygenation; EVLP, Ex vivo lung perfusion; ICU, Intensive care unit; LAS, Lung allocation score; LFTs, Liver function tests; MAP, Mean arterial pressure; MELD, Model for end-stage liver disease; OLT, Orthotopic liver transplant; PPHTN, Portopulmonary hypertension; PGD, Primary graft dysfunction; RV, Right ventricle; SVR, Systemic vascular resistance; TEE, Transesophageal echocardiogram; THAM, Tris(hydroxymethyl)aminomethane; VVB, Venovenous bypass.

* Corresponding author at: OSU Wexner Medical Center, 395 W 12th Ave, Suite 150, Columbus, OH 43210-1267, United States.
E-mail address: Sylvester.Black@osumc.edu (S.M. Black).

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largely comprised of single or two patient case studies; the largest published cohort is a single-center study by the Hannover group (Salman, n = 25), followed by single-center US groups (Arnon, n = 15; Barshes, n = 11; Yi, n = 8) [3–6].

Despite its rarity, CLLT serves as a last recourse for those patients with end-stage lung disease complicated by concomitant liver disease, in whom survival is not expected with single organ transplantation alone. Combined liver-lung transplantation is most commonly indicated in cystic fibrosis accompanied by cirrhotic liver disease [7]. Given the limited experience with CLLT, there is immense variability in patient cohort, selection criteria, surgical technique, anesthesia protocols, and postoperative management. Moreover, posttransplant immunosuppressive protocols tend to vary from center to center, and in light of the ever-growing understanding of transplant immunobiology, the pattern of induction and maintenance therapy continues to change [8,9]. This review examines the current literature regarding combined liver-lung transplants, most of which were retrospective case series or single transplant center analyses. Though this necessarily limits the generalizability of recommendations, we review the existing medical literature and discuss the indications, procedure, and outcome to assist clinicians in evaluating patients for CLLT.

2. Indications

Associated conditions such as hepatopulmonary syndrome and portopulmonary hypertension exemplify the complex relationship between liver and lung, wherein common sequelae of primary pathologies of either organ include a heterogeneous group of complications for the other [10]. As such, combined transplant candidates comprise a diverse patient cohort of both pediatric and adult patients with congenital or acquired disease [10]. Indications for CLLT include end-stage lung disease with concomitant liver disease, such as cystic fibrosis (CF) and α1-antitrypsin deficiency, or end-stage liver disease with pulmonary compromise, as in the case of portopulmonary hypertension or cirrhosis-related hypoxemia with intrapulmonary shunting (Table 1) [5]. In a single center analysis of eight consecutive CCLT patients, pulmonary indications included CF, idiopathic pulmonary fibrosis, α1-antitrypsin deficiency, and pulmonary hypertension; liver indications included CF, hepatitis C, α1-antitrypsin deficiency, portal hypertension, cryptogenic, and cardiac/congestive [6,7]. The distribution of these indications has changed over time, as identified in a recent retrospective analysis separating early clinical from modern era experience with CLLT. This separation was defined as mid-2005 with implementation of the Lung Allocation Score (LAS), which prioritizes medical need over wait-time. The primary indication for lung transplant was cystic fibrosis, while the second most prevalent indication has shifted from primary pulmonary hypertension (40% pre- vs 0% post-2005 patients) to idiopathic pulmonary fibrosis (0% pre- vs 17.3% post). The indications for liver transplant remain primarily cystic fibrosis followed by cirrhosis [11]. Current literature describes recipients ranging from 10 to 55 years old, suggesting a possible bimodal distribution of younger patients in their mid-teens with genetic disease, and older adults in the 40 to 50s with separate lung and liver pathology [5–7,12–14]. Irrespective of primary lung or primary liver disease, the decision to pursue combined liver-lung transplant is made when the patient is deemed unable to tolerate isolated transplant of either organ alone [6,7].

Cystic fibrosis remains the most common indication for CLLT. Morbidity and mortality of CF patients is usually associated with pulmonary complications and end-stage lung disease, though liver disease is a frequent independent prognostic factor and has been cited as the second leading cause of death among these patients [4,13,15]. A 27–35% cumulative incidence of liver disease before 18 years of age has been reported in long-term follow up of different CF patient cohorts, with approximately 5–10% of all CF patients developing multilobular cirrhosis during the first decade of life [14,16]. Other studies have reported the incidence of multilobular cirrhosis to be up to 20–30% in CF patients [5]. Though the mainstays of medical management involve preventing disease progression and bleeding episodes, CF patients are at increased risk of variceal hemorrhage or complications of end-stage liver disease, and a decline in pulmonary function is an important consideration when deciding to pursue orthotopic liver transplantation (OLT) [4,16]. Improved pulmonary outcomes in CF patients have been shown to follow liver transplant [17,18]. While selection criteria and timing for OLT in CF patients remains a matters of clinical judgment, both hepatic and extrahepatic parameters are important considerations, the latter including progressive deterioration of nutritional support and pulmonary function [16]. Patients with significant lung destruction may be unable to

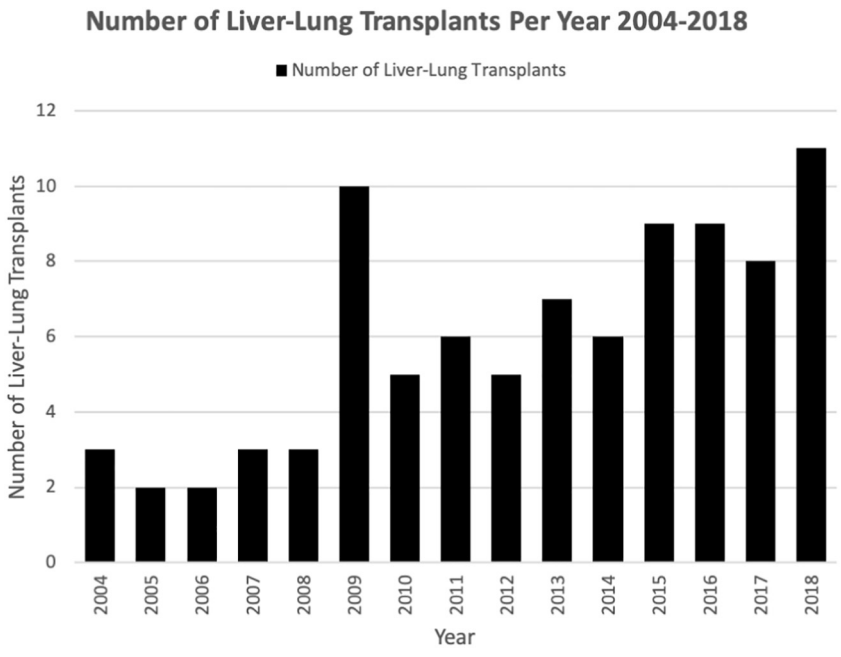

Fig. 1. Number of Liver-Lung Transplants Per Year 2004–2018.

Table 1
Indications for combined lung and liver transplant.

Indications for combined lung-liver transplantation (CLLT)	
Cystic fibrosis [3–7,12–14,18–20,24,41]	
Alpha 1-antitrypsin [5–7,19]	
Sarcoidosis [7]	
Indications for lung portion	Indications for liver portion
Cirrhosis related hypoxemia with intrapulmonary shunting [5]	Hepatitis C cirrhosis [6]
	Cryptogenic cirrhosis [6]
	Alcoholic cirrhosis [19]
PPHTN [5–7,40,60]	Cardiac/congestive [6]
COPD [27]	Viral hepatitis [60]
Idiopathic pulmonary fibrosis [6,19]	Acute hepatic failure [27]

tolerate isolated liver transplant, while severe portal hypertension and impaired liver function may preclude isolated lung transplant. Under these circumstances, CLLT may be required in order to achieve meaningful improvement of life [5,7,14].

3. Patient candidacy

There is limited description of appropriate pre-transplant evaluation of patients requiring CLLT, though the typical approach is independent evaluation for each organ. Most authors describe CF patients with known bacterial colonization [12–14] who presented with severely compromised pulmonary function requiring supplemental oxygen or mechanical ventilation, and liver complications such as history of gastrointestinal bleed [14]. Yi et al. report that CLLT candidacy was first determined with the criteria for lung transplantation, with subsequent liver transplant candidacy based on biopsy-proven cirrhosis and portal gradient ≥10 mmHg. Approval for dual listing was made by a multidisciplinary board review and candidates were listed according to recipient Lung Allocation Score (LAS, median 41) and Model for End-Stage Liver Disease score (MELD, median 9.5), with transplant candidacy overall based primarily on LAS [6]. A few centers report candidate participation in preoperative pulmonary rehabilitation with regular intensive physiotherapy, as well as parenteral nutrition or jejunostomy feeding while on the waitlist [12,14]. Duke University Medical Center describes a protocol in which the transplant infectious disease service follows patients preoperatively, and all lung recipients with CF receive a minimum 3-weeks of antibiotics against pre-transplant colonizing organisms [19].

4. Operation

While there are proposed variations to the surgical approach and anesthesia protocols for CLLT, the sequence of transplantation for all reviewed studies were lungs first, followed by liver from the same donor. Coordination of the thoracic abdominal teams is critical in the process of operative planning. Lungs were preserved in low potassium dextran solution (Perfadex) and liver in University of Wisconsin solution (UW) [6,12]. The commonly described technique is to perform sequential bilateral lung transplant with selective use of cardiopulmonary bypass (CPB), leaving the chest open, and performing the liver transplant with selective use of venovenous bypass (VVB). Lung transplant through a midline sternotomy [14] or via anterolateral mini-thoracotomies [6,7] has been described. The decision to use CPB depended on the clinical status of the recipient, namely in the setting of severe pulmonary hypertension precipitating significant right heart dysfunction or failure, hemodynamic instability, and global hypoxia. This was usually followed by reversal of heparinization prior to liver transplant, and procedures were otherwise performed without extracorporeal circulation during both thoracic and abdominal portions [7,12,14]. One case report described initiating extracorporeal membrane oxygenation (ECMO) with low-dose heparinization as a successful alternative to CPB in a patient with only transient right heart insufficiency, citing its efficacy, ease of implementation, and transferability from operating room to ICU [20]. However, studies regarding outcomes of intraoperative ECMO versus traditional CBP during isolated lung transplantation have reported conflicting results, and more data is needed before a standard for extracorporeal circulation can be established for CLLT [21,22].

Several methods for biliary reconstruction have been described, including choledochocholedochostomy, hepatico-choledochostomy, roux-en-Y hepaticojejunostomy, and roux-en-Y choledochojejunostomy. Couetil et al. argue that roux-en-Y choledochojejunostomy decreases the risk of biliary duct stricture, and have reported instances where choledochocholedochostomy resulted in bile duct stricture necessitating laparotomy with conversion to roux-en-Y choledochojejunostomy [7,14,19,23]. Data to support whether this poses a real risk is limited to anecdotal evidence. Couetil et al. also chose to close the chest before proceeding with the biliary anastomosis in order to minimize risk of contamination [14]. Closure of the abdomen first followed by re-inspection of the chest for hemostasis and then closure of the chest last has also been described [13].

Center-specific modifications to the operation have been reported over time. Grannas et al. describe initially using a staged approach with an interim 2 to 4-h period in the intensive care unit between lung and liver transplants, for the purpose of respiratory and circulatory stabilization. This was subsequently obviated with the use of Perfadex, which the authors state appeared to address the issue of reperfusion edema [7]. By 2011, Yi et al. chose to proceed with abdominal dissection prior to both lung and liver implantation in order to minimize the transfusion of blood products, volume overload, and pulmonary edema in the newly transplanted lung [6]. Other strategies have been employed as a response to the logistical challenges of waiting for two available organs. Van de Wauwer describe a staged approach in which the authors first performed high-urgency transplantation of ex vivo reconditioned lungs from an unsuitable donor after circulatory death, followed by successful urgent liver transplantation 19-days later when the patient developed an acute-on-chronic liver failure [24].

The preferred sequence of combined lung and liver transplantation has been lung first, as the lung is believed to be more ischemic time sensitive than the liver. However, primary graft dysfunction is frequently encountered secondary to coagulopathy, hemodynamic instability, and volume and transfusion requirement associated with OLT [13]. More recent retrospective case studies have suggested that the lungs are more robust than previously believed, and in conjunction with techniques such as ex vivo lung perfusion (EVLP), may obviate the need for a lung-first sequence. EVLP splits one long cold ischemic time into two shorter periods by interposing an additional EVLP time [25]. Grimm et al. examined 10,225 lung transplantation patients, 30.6% of whom received allografts exposed to prolonged ischemia (≥6 h), and found that prolonged ischemia did not independently predict 1-year (hazard ratio 1.09; 95% CI, $p = 0.15$) or 5-year (HR 1.05; 95% CI, $p = 0.18$) mortality, or the development of primary graft failure (odds ratio 1.11; 95% CI, $p = 0.37$) [26]. Yeung et al. subsequently examined 906 lung transplant patients, 97 of whom underwent transplantation with total preservation time > 12 h (mean 875.7 min [SD 109.0]) and found no difference in median hospital and ICU length of stay or primary graft dysfunction (PGD) grade at 72 h post-transplantation [25].

There have been isolated case reports of liver first CLLT, with anecdotal data suggesting that it may be a non-inferior technique. Salman et al. report a series of 25 patients who underwent same donor CLLT between 1999 and 2015, during which time the group reversed the sequence of transplant to liver first, in 2008. The 8 patients who subsequently underwent liver transplant followed by bilateral sequential lung transplant were reported to have shorter ICU and hospital stays compared to the lung first group (liver first 9 ± 9, 39 ± 17 days vs. lung first 20 ± 21, 68 ± 63 days; $p < 0.05$), as well as improved 1 and 5-year survival (liver first 73%, 73% vs. lung first 65%, 47% [3]. Ceulemans et al. described choosing to transplant liver first in an end-stage COPD

patient with acute onset drug-induced liver failure, in order to correct coagulopathy and reduce perioperative bleeding risk. To address the issue of longer lung preservation time, cold flushed lungs were preserved with ex vivo normothermic perfusion [27,28]. The theoretical advantages of this sequence reversal are proposed to be 1) reduced edema in the new lung, 2) reduced transfusion requirements through correction of coagulopathy, and 3) reduced risk of biliary stricture secondary to shorter liver cold ischemia time [28,29]. While these are compelling theoretical benefits to a liver-first approach, it remains to be seen if these results persist as the cohort size increases, and if they can be replicated at other institutions. Ultimately, the decision-making relies on case-by-case evaluation of organ-specific disease severity. In general, it is reasonable to consider transplanting the sickest organ first, in order limit the risk of remote organ injury or sepsis [29].

5. Perioperative challenges and complications

CLLT presents a particular challenge for anesthesia, as the liver and lung transplant have opposing anesthetic goals regarding optimal volume resuscitation and ventilation (Table 2) [13]. Therefore, cooperation and coordination between teams is essential for operative success. Post reperfusion syndrome is a well-established intraoperative complication of liver transplantation, defined as a decrease in mean arterial pressure (MAP) >30% below baseline and lasting for at least 1-min during the first 5-min of liver graft reperfusion. Both profound cardiovascular and metabolic shifts occur as the hepatic hilum is unclamped, with the sudden influx of cold, acidotic, hyperkalemic fluid and reactive oxygen species from the new ischemic liver, a dramatic decrease in systemic vascular resistance, and an increase in pulmonary artery pressure [30]. The right ventricle (RV) is particularly vulnerable to acute intraoperative failure in the CLLT recipient due to intrinsic pulmonary disease. These patients often have pulmonary hypertension with pre-existing abnormalities in ventricular septal function and increased sensitivity to myocardial stunning. The loss of lymphatic drainage, oxygen toxicity, and transfusion related lung injury in the newly transplanted lung therefore necessitates more conservative fluid management, which is associated with improved lung function though may otherwise be insufficient to maintain adequate organ perfusion [13,31–33].

Several strategies to prevent post reperfusion syndrome or to minimize RV dysfunction have been proposed, though the evidence is largely culled from retrospective single-center and case studies. These strategies include volume resuscitation with colloid infusion to optimize RV preload, tris(hydroxymethyl)aminomethane (THAM), and pretreatment with adrenergic agonists to increase systemic vascular resistance [13]. More aggressive red blood cell transfusion to a goal hematocrit >26% has been suggested in lieu of resuscitation with crystalloid in order to maintain adequate intravascular volume and prevent AKI, and the use of intraoperative TEE has been recommended to guide fluid management [13]. In the context of liver transplantation, administration of methylene blue is thought to improve SVR, MAP, cardiac contractility, and graft function by reducing production of nitric oxide, thereby decreasing need for adrenergic support [30]. Additionally, administration of nitric oxide in the setting of lung transplantation has been suggested to improve gas exchange and oxygenation, thus improving allograft function and preventing early allograft failure [34]. In the event that extracorporeal circulation is required during lung transplant, epsilon-aminocaproic acid (EACA) has been used for antifibrinolysis prior to CPB as it is associated with decreased blood loss and RBC transfusion requirement [13]. More evidence is required to support the role of these agents as additional therapy during CLLT. Reasonable strategies include volume loading, THAM administration, calcium chloride repletion, and use of adrenergic agonists [13]. From an operative standpoint, Yi et al. suggest first completing abdominal dissection of the liver with necessary product administration while the old lungs are in place followed by the lung transplant, and subsequently returning to complete the liver transplant. Postoperatively, fluid restriction and vasopressor support were titrated to MAP ≥65 mmHg, with median CVP of 8.5 (Range 4–17) and median Pulmonary Artery Pressure of 22.3 (Range 14.3–27) [6].

Postoperative renal dysfunction is common after lung transplantation, secondary to preoperative respiratory failure, renal hypoperfusion during cardiopulmonary bypass, and postoperative use of calcineurin inhibitors and diuretics [13,35]. Additional complications that have been reported include: surgical complications due to injury, anastomotic failure or subsequent stricture, bile duct ischemia, bile leak, necrotizing pancreatitis with subsequent duodenal perforation, acute rejection, idiopathic thrombocytopenic purpura, and most commonly bacterial and viral infection [6,7,19]. CF patients receiving CLLT were particularly susceptible to infectious complications given the high rate of both preoperative and de novo colonization [6]. At Duke University Medical Center, no infections by pre-transplant colonizing organisms were reported in posttransplant CF patients in the setting of an established pre-transplant antibiosis protocol. Rather, the majority of infections were due to nosocomial pathogens including vancomycin-resistant enterococcus, *Candida* species, and *Clostridium difficile* [19].

6. Follow up, maintenance, and surveillance

There are few descriptions regarding specific postoperative maintenance and surveillance regimens. Grannas et al. report regular follow up in outpatient clinics with routine labs, chest radiographs, pulmonary function tests, and abdominal ultrasound evaluation [7]. Yi and colleagues performed surveillance bronchoscopy weekly until one month, followed by every 2-weeks for three months, then every month for a year [6]. Characteristic changes in LFTs with histologic confirmation have been used for diagnosis of liver allograft rejection while rejection of the lung allograft was diagnosed from the presence of worsening lung function, exclusion of other infectious or structural etiologies, and response to steroid treatment [7]. These are practices from single institution reports now nearly a decade old. With the advent of new immunosuppression and antimicrobial prophylaxis, it is difficult to conceive of weekly bronchoscopies. There have been studies of non-invasive options or biomarker surrogates for monitoring infection and rejection following solid organ transplant that have not been confirmed clinically [36,37]. The current gold standard for diagnosis of acute rejection following lung transplant remains transbronchial biopsy [36]. The gold standard for diagnosis of acute cellular rejection in liver transplant is also biopsy, and although donor specific antibody (DSA) has been associated with progressive fibrosis and antibody-mediated rejection, there has yet to be direct linking of posttransplant DSA positivity with liver tissue injury [38]. The threshold for performing invasive procedures to obtain histopathology samples, cell counts, and cultures for diagnosis of infection are necessarily lower in post-transplant patients, who demonstrate diminished inflammatory responses such as fever and localizing signs. Effort should be made to establish specific microbiologic diagnoses to optimize therapy and decrease the incidence of drug toxicity and multidrug resistance [39].

The immunosuppression regimen most commonly reported in literature is based on the regimen following lung transplant. Induction protocols generally involve some combination of a steroid and mature T cell-targeting monoclonal antibody, such as methylprednisolone with or without daclizumab or basiliximab [6,19], or a regimen of mycophenolate mofetil (MMF) followed by three doses of methylprednisolone and three days of anti-thymocyte globulin (ATG) [27]. Induction with single agents such as alemtuzumab only [40], or with a triple therapy of steroids, tacrolimus, and basiliximab [7,41] have also been described. Several studies achieve maintenance with MMF, a steroid taper, and tacrolimus, with a target serum tacrolimus trough of 10–12 ng/mL [5,6,12,19]. Ceulemans et al. targeted a trough level of 12 for their case series of 14 combined liver-thoracic transplantation (including liver-heart, liver-heart-lung), while Scouras et al. targeted a lower serum tacrolimus trough of 8–10 ng/mL in their single CLLT patient, and reported

Table 2
Anesthetic goals of lung vs liver transplant [13,33,61].

Anesthetic goals	Lung transplant [13,31,33]		Liver transplant [13,61,62]		Combined lung-liver
	Concern	*Management*	*Concern*	*Management*	
Hemodynamic	Increased sensitivity to hypervolemia 2/2 absent lymphatic drainage, O2 toxicity, TRALI	Fluid restriction to maintain low CVP > 5 mmHg	Reperfusion syndrome	Maintain higher CVP[a]	
Cardiac	Perioperative RV dysfunction 2/2 pulmonary HTN, ESPD	Inotropes, judicious volume administration, inhaled NO or epoprostenol, TEE to assess real-time RV function	Perioperative low SVR state 2/2 ESLD, reperfusion syndrome, ROS release from ischemic liver	Alpha-agonists, aggressive colloid resuscitation[a], NaHCO3, THAM, CaCl, methylene blue	- Judicious volume administration - THAM
Pulmonary	Prevent PGD in early postoperative period	Low TV (6 mL/kg), PEEP (5–15 cmH2O), low FiO2, low PCWP, inhaled NO	Presence of intrapulmonary shunts 2/2 portopulmonary HTN, hepatic hydrothorax	100% FiO2 may be necessary	- Adrenergic agonists to increase SVR
Ventilation	Avoid barotrauma, dynamic hyperinflation	Permissive hypercapnia	Avoid respiratory acidosis	Aggressive ventilation[a]	- TEE to guide volume resuscitation
Gastrointestinal	Uncommon to have periop issues	TEE to assess pulmonary anastomosis	Esophageal varices, ascites, and gastropathy common; increased aspiration risk	Consider TEE versus bleeding risk; rapid sequence inductions	- Maintain lowest Hct > 25%
Coagulation	Prevent hypervolemia, TRALI	Limited blood products	Coagulopathy from PLT dysfunction, decreased factor synthesis, vit K deficiency; DIC; risk for hepatic artery thrombosis	Aggressive resuscitation with multiple blood products with uncontrolled bleeding only, EACA antifibrinolysis, correct calcium and potassium derangements	- Limit transfusion of coagulation factors - Correct metabolic derangements
Renal	Renal failure 2/2 preoperative respiratory failure, intraop hypoperfusion during CPB	Avoid perioperative anemia	Renal failure 2/2 hepatorenal syndrome	Preop vasoconstrictors; consider combined liver-kidney transplant	
Postoperative pain control		Thoracic epidural	Periop coagulopathy is contraindication to epidural	Regional blocks, oral and intravenous medications	

Abbreviations: DIC, disseminated intravascular coagulation; TV, tidal volume; PEEP, positive end-expiratory pressure; SVR, systemic vascular resistance; ROS, reactive O2 species; ESPD, end-stage pulmonary disease; NO, nitric oxide; PCWP, pulmonary capillary wedge pressure.
[a] Especially before reperfusion.

no episodes of lung or liver rejection in 18-months following transplant [28,40]. Azathioprine and everolimus have also been used as part of maintenance therapy in order to reduce the tacrolimus trough level in an effort to preserve renal function [41].

It has been suggested that target levels of immunosuppression can be lowered in CLLT compared to single organ transplant, as same donor liver allografts have been postulated to confer immunologic protection to other simultaneously transplanted organs [6,28,42–47]. In the case of combined liver-kidney transplant, cross-match has been shown to turn negative following liver transplant in highly sensitized patients, with reduced renal allograft rejection rates at 1-year [48]. A small case series of five pediatric CLLT recipients showed lower rates of acute rejection and bronchiolitis obliterans syndrome compared to recipients of isolated lung transplants [49]. A case study of four adult CLLT recipients demonstrated similar, though transient, immunologic advantage, with liver-lung transplants remaining rejection free at significantly lower levels of tacrolimus [47]. One proposed mechanism for this immunologic privilege is a myeloid-mediated suppressive network in the liver resulting in activation of regulatory T cells with suppression of CD8+ and CD4+ T cells by liver antigen-presenting cells [50]. Alternatively, it has been posited that the liver is able to neutralize lymphocytotoxic antibodies, or that the increased antigen load of multiorgan transplant is able to confer immunologic protection [42,48]. Reports of early mortalities are attributed to sepsis, rather than rejection, and episodes of rejection were commonly treated successfully with steroids [6,7,27,41]. Further investigations are needed to determine the optimal immunosuppressive regimen following CLLT.

CLLT recipients often have chronic colonization, given the preponderance of cystic fibrosis as the underlying lung pathology. Three months of continued antibiotic therapy following CLLT has been recommended for all chronically colonized patients [6]. Grannas et al. describe an antibiotic prophylaxis regimen that includes inhalational and topical amphotericin B in the post-operative period, ceftazidime/tobramycin/flucloxacilline for a minimum of 10-days, followed by lifelong 800/160 mg trimethoprim/sulfamethoxazole twice per week and lifelong oral itraconazole. Patients with risk profile for CMV also received 1 month of IV ganciclovir followed by a 6-month course of oral acyclovir; in the event of high-risk CMV status, or those with CMV reactivation or de novo CMV infection, patients received lifelong prophylaxis with valgancylovir [7]. Universal prophylaxis has not been studied in the CLLT cohort, however lifelong prophylaxis in recipients at risk for primary infection is not the standard of care per practices following single organ donation. Universal prophylaxis involves administering antivirals to all or “at risk” patients starting within 10-days post-transplant for a finite period of 3 to 6-months, with valganciclovir used most commonly. At this time, it is reasonable to place CMV D+/R- patients on prophylaxis for 3 to 6-months after liver transplantation and for 1-year in lung transplant recipients. Testing for CMV DNAemia is not recommended during routine prophylaxis and the gold standard for diagnosis of tissue-invasive disease is identification of CMV cytopathic changes or CMV antigens by immunohistochemistry [39,51]. There is insufficient data to support routine use of antiviral prophylaxis in the EBV D+/R- population [39].

Targeted prophylaxis against *Candida* infections has been applied to liver recipients, which has been observed posttransplant in the setting of cholangitis, bile leaks, and hematomas, with increased risk in the setting of choledochojejunostomy over duct-to-duct anastomosis [39]. Pulmonary candidiasis is rare outside of tissue infarction, such as at the tracheal anastomoses in lung recipients [39], and inhaled amphotericin B has been shown to be safe and efficacious during the early 6-month

posttransplant period [52]. *Aspergillus* infection is observed most commonly in lung recipients, with >25% colonization rate and a nearly 6% rate of invasive infection that is further increased in the setting of cystic fibrosis. Diagnosis requires bronchoalveolar lavage or biopsy for cultures. At least 4-months of universal voriconazole prophylaxis has been recommended to reduce risk of invasive fungal disease based on observational study. It has been suggested that 85-days to 4.2-months of preemptive treatment of mold-active azole therapy results in lower incidence of invasive disease, although long-term voriconazole use has been associated with development of squamous cell carcinoma and periostitis [52]. Lung transplant patients maintain a lifelong risk of *Pneumocystis jiroveci* pneumonia for which low-dose trimethoprim/sulfamethoxazole prophylaxis remains standard of care [39].

The relationship between immunosuppression and infection risk is known, though the synergy of different immunosuppressive agents and host response to pathogens still requires investigation. Fishman describes a relatively predictable timetable of infection that is observed in the setting of most standardized immunosuppressive regimens, which reflects the changing risk factors in the post-transplant course. In the first month post-transplant, infections reflect technical issues (e.g. bleeding, graft injury), pre-existing recipient or donor-derived infections, and nosocomial exposures. This changes at 1 to 12-months posttransplant to the many infectious syndromes that may represent graft rejection, viral, or opportunistic infections in the setting of variable prophylaxis. Beyond a year, patients with functioning allografts tolerate reduced maintenance immunosuppression with associated lower risk of infection, and therefore begin to demonstrate infections reflecting community-based epidemiological exposures. Patients deviate from this timeline when they have tenuous graft function requiring higher levels of maintenance suppression, and constitute a high-risk group that may benefit from lifelong viral and antifungal prophylaxis [39].

7. Outcomes

Arnon etal. examined outcomes of combined liver and lung transplants in patients with CF and found that patient and graft survival at 1- and 5-years for isolated lung transplant and CLLT were comparable (patient survival: LT 83.9%, 75.7% versus CLLT 80%, 80%; graft survival: LT 76.1%, 67% versus CLLT 80%, 80%) [4]. Similarly, patient survival after CLLT versus OLT are also reported to be comparable at 30-day, 1-, 3- and 5-years (CLLT: 79%, 79%, and 63% versus OLT: 83.2%, 76.4% and 71.1%; $p = 0.59$) [5], results of which were corroborated by Desai et al. CLLT: 72%, 61.4%, and 61.4% versus OLT: 80%, 74%, and 67%; ($p = 0.7$) [18]. Among the largest single institution published studies, reports of patient survival at 1-year range between 65 and 92% [3,6,7,19,28]. (Table 3) In the most recent published study, 75% of recipients experienced at least minimal acute cellular rejection of their lung allografts over a two decade long period, with an average 0.68 incidence of acute rejection per year in which 96.9% involved acute cellular rejection to 3.1% antibody-mediated rejection; no episodes of acute or chronic liver rejection were reported [19]. Of deceased patients, causes of death included primary liver graft failure, decompensated liver disease from recurrent viral infection, bronchiolitis obliterans syndrome, bacterial or viral sepsis with organ failure, or stochastic processes (e.g. oncologic disease, accident, ruptured aneurysm, stopping immunosuppressive therapy against physician advice) [6,7,19].

8. Conclusion

Combined lung-liver transplantation necessitates mobilization and coordination between two organ transplant programs in order to optimize patient outcomes. Pulmonary and liver failure secondary to cystic fibrosis remains the most common indication for combined thoracic organ-liver surgery, which poses specific challenges as these patients are higher risk surgical candidates given their complex multisystem disease processes. The perioperative pulmonary and hepatic insults, followed by long term immunosuppression in often perpetually colonized and malnourished patients, creates a precarious operative environment that requires prudence and vigilance from both surgeon and anesthesiologist. Yet patient outcomes for isolated organ transplant and combined lung-liver transplant have been shown to be similar. Moreover, there is a growing body of literature describing a variety of successful operative techniques and options that carefully consider patient-specific factors to improve outcomes. Modalities like ECMO and ex-vivo lung perfusion are now available to further stretch the bounds of recipient candidacy for combined transplant; this pool will only increase as current therapies for primary lung and liver disease improve as well [53].

In 2016, 2692 new candidates were added to the United States lung transplant waiting list, with a median waiting time of 2.5 months and a record high of 2345 transplants performed. Transplant rates for group C patients (i.e. CF and immunodeficiency disorders) increased more so relative to rate increases in other diagnosis groups, representing 12.3% of transplants with a median revised LAS of 43.3 among recipients [54]. As of December 31, 2016, a total 11,140 active candidates were on the liver transplant waiting list, with 7841 transplants performed for recipients with MELD scores most commonly falling between 15 and 29 [55]. Within those numbers, a total of nine combined liver-lung transplants were performed that year. While organ allocation policy for CLLT, given its rarity, has not been finessed like its kidney-liver counterpart, it is nevertheless necessary to develop criteria for appropriate selection and timely listing of patients [56]. Yi et al. has suggested that CLLT should be considered for patients with LAS < 50, who do as well as single- or double-lung transplants with equivalent LAS [6]. Ceulemans' combined liver/thoracic transplantation patient cohort had a median lab-MELD of 12 [28] while Freischlag's post-2005 modern era patients had a mean LAS of 50.78 and mean MELD-XI (MELD excluding INR) of 11.48 [11]. Both LAS and MELD scores are used to prioritize organ allocation for transplant: higher scores indicate higher priority, with higher LAS indicating greater expected survival benefit and higher MELD scores indicating worse waiting list mortality and prognosis. It follows that candidates for multiorgan transplant have higher waiting list mortality than their counterparts with single organ disease and similar LAS or MELD scores, and transplantation confers significant survival benefit [28]. Waitlist survival at 1- and 3-years for simultaneous lung-liver transplants has been shown to be lower than single-organ controls (65.7%, 41.0%, $p < 0.001$) while posttransplant survival is comparable to thoracic transplantation controls [57].

In the setting of organ scarcity, how organ allocation can most equitably be performed becomes a philosophical question. Reese et al. nicely describe the components of philosopher John Rawls' theory of justice as the guiding principles behind organ allocation to transplant candidates. First, patients should have equal access to organs (a tenet that is violated by multiorgan transplant recipients receiving higher priority for their additional organs) and second, imbalances should only exist to benefit the least advantaged in society (for which there is currently no clear metric to compare 'least advantaged') [58]. The goal of organ allocation policy reform should therefore be to reduce discrepancies in waiting list survival among transplant candidates, while not prioritizing multiorgan transplant allocation above single organ transplants, and also avoiding futile transplants. This issue is further complicated by the variability of allocation practices depending on the organ combination in question, as the provisions for allocation changes depending on the perceived medical urgency of the individual organs in each combination. In the case of CLLT, patients with a high LAS but relatively lower MELD score will bypass the liver-only patient with high MELD score, presumably resulting in higher waitlist mortality for the latter. As there is a higher incidence of chronic lung allograft rejection compared to isolated liver, is this a judicious and pragmatic use of resources? Goldberg et al. examined Organ Procurement and Transplantation Network data from 2007 to 2013 to evaluate the impact of combined heart-lung organ allocation policy on bypassed liver waitlist candidates. They concluded that the

Table 3
Outcomes of combined liver-lung transplantation.

Author (Year)	Location	Timeline	Patients	Indications		Rejection	Survival (%)		
				Liver	*Lung*		*1 year*	*3*	*5*
Couetil (1995)	France[b]	1990–1995	5	CF	CF	–	70	70	
Zimmerman (1999)	USA[b]	–	1	ESLD 2/2 focal biliary cirrhosis	CF	–	–	–	–
Pirenne (2002)	Belgium[b]	1994	1	Active HCV	PPHTN	–	Death within 24 h Cardiac failure		
Barshes (2005)	USA	1987–2004	12	CF	CF	3 (lung)	79	63	63
Corno (2007)	Italy[b]	2002–2006	3	CF	CF	1 lung	100	–	–
Grannas[a] (2008)	Germany	1993–2003	12	CF (5), AATD (2), sarcoidosis (1), PHTN (5)	CF (5), AATD (2), sarcoidosis (1), PHTN (5)	3 (liver) 5 (lung)	69	62	49
Moreno Casado (2008)	Spain[b]	–	2	CF	CF	–	Pt 1: survival at 3y FU Pt 2: survival at 9 m FU		
Scouras (2011)	USA[b]	–	1	HCV	PPHTN	–	Survival at 18 m		
Arnon (2011)	USA	1987–2008	15	CF	CF	–	80	–	80
Desai (2013)	USA	1987–2009	(A) 21 (P) 8	CF	CF	7 (liver, adult)	72 83	61.4 83	61.4 83
Adams (2013)	USA[b]	–	1	HPS	CF	–	–	–	–
Yi[a] (2013)	USA[b]	2009–2012	7	CF (3), HCV (2), AATD (1), cryptogenic cirrhosis (1), cardiac/congestive	CF (3), IPF (2), AATD (1), PHTN (2)	1 (lung)	71.4	–	–
Ceulemans (2014)	Belgium[b]	–	1	Drug-induced ALF	End-stage emphysema	–	–	–	–
Ceulemans (2016)	Belgium[b]	2000–2015	10	CF-cirrhosis (5), EHE (2), drug-induced ALF (1), ethyl cirrhosis (1), NASH cirrhosis (1)	CF (5), EHE (2), COPD stage IV (1), HPF (2)	1 (liver) 4 (lung)	≥5y (4), ≥ 1y (2), ≥1 m (4) All patients surviving on FU, most recent transplants in 2 015 (4)		
Van de Wauwer (2015)	The Netherlands[b]	–	1	CF	CF	–	–	–	–
Scheiermann (2015)	Germany[b]	–	1	CF	CF	–	100	–	–
Salman (2016)	Germany[b]	1999–2015	Lung first: 17 Liver first: 8	main indications: CF and PHTN		–	65 73	– –	47 73
Freischlag (2018)	USA[b]	2000–2016	12	CF (8), idiopathic cirrhosis (2), EtOH cirrhosis (1), AATD (1)	CF (8), IPF (3), HPF (1)	1 (liver) 3 (lung)	91.7	71.3	–

Abbreviations: A, adult; ALF, acute liver failure; EHE, epithelioid hemangioendothelioma; EtOH, alcoholic; FU, follow up; HPF, hepatopulmonary fibrosis; IPF, interstitial pulmonary fibrosis; NASH, nonalcoholic steatohepatitis; P, pediatric; PHTN, pulmonary HTN; PPHTN, portopulmonary HTN.
[a] Aggregate data including combined liver-heart-lung transplants were separated when possible, otherwise excluded.
[b] Single center.

latter, as a group, did not demonstrate increased waitlist mortality or risk of waitlist drop off [59]. However, their analysis does not examine the utility and overall yield in quality-adjusted life-years of allocating multiple organs to a single recipient instead of single organs to multiple recipients. As the number of simultaneous organ waitlist candidates continues to grow, it will become necessary to develop a more rigorous multiorgan allocation policy. Further investigation is required to determine not only optimal patient candidacy and allocation methodology, but ongoing improvement in operative technique and immunosuppressive maintenance following CLLT.

Conflict of interest

None of the authors received remuneration, reimbursement, or honorarium in the production of this manuscript and have no conflicts of interest to report.

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